JX29

Original Article

Blood pressure and kidney cancer risk: meta-analysis of prospective studies

Khemayanto Hidayat, Xuan Du, Sheng-Yi Zou, and Bi-Min Shi

Background: Globally, kidney cancer is the twelfth most common cancer, accounting for 337 860 cases recorded in 2012. By 2020, this number has been estimated to reach 412 929 or increase by 22%. Over the past few decades, a number of prospective studies have investigated the association between blood pressure (BP) and risk of kidney cancer, using either recorded BP levels or reported hypertension as the principal exposure variable. However, the relation of BP to kidney cancer remains incompletely understood, and the data on sex-specific differences in risk estimates have been inconsistent.

Method: PubMed and Web of Science databases were searched for studies assessing the association between BP and kidney cancer through July 2016. A total of 18 prospective studies with 8097 kidney cancer cases from 3 628 479 participants were included in our meta-analysis.

Result: History of hypertension was associated with 67% increased risk of kidney cancer. Significant heterogeneity and evidence of publication bias were observed. However, the results remain unchanged after introducing the trim and fill method to correct the publication bias. Accordingly, each 10-mmHg increase in SBP and DBP was associated with 10 and 22% increased risks of kidney cancer.

Conclusion: Collectively, the present meta-analysis of 18 prospective studies provides further support for a positive association between hypertension and kidney cancer.

Keywords: dose–response, hypertension, kidney cancer, meta-analysis, renal cell carcinoma

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, relative risk

INTRODUCTION

Globally, kidney cancer is the twelfth most common cancer, accounting for 337 860 cases recorded in 2012. By 2020, this number has been estimated to reach 412 929 or increase by 22% [1]. The observed rise in kidney cancer incidence may partly be accounted by improved detection by use of ultrasound and MRI [2]. The prevalence of kidney cancer is twice as high among men than women, and more than 50% of kidney cancer cases occurred in more developed countries, with the highest rates being recorded in North America and Europe and the lowest in Asia and Africa [1,3,4]. This indicates that genetic and environmental factors associated with Western lifestyle may play a role in the development of kidney cancer [5]. Hypertension, obesity, and smoking are well established lifestyle-related risk factors for kidney cancer [6–10]. Over the past few decades, a number of prospective studies have investigated the association between blood pressure (BP) and risk of kidney cancer, using either recorded BP levels or reported hypertension as the principal exposure variable [11–28]. However, the relation of BP to kidney cancer remains incompletely understood, and the data on sex-specific differences in risk estimates have been inconsistent [14,16,20,21,23,25]. Furthermore, the association between BP and kidney cancer risk has not been comprehensively summarized in a quantitative meta-analysis, and the exact shape of the dose–response relationship between BP and kidney cancer risk has not been clearly defined. Thus, providing further clarification of potentially detrimental effect of high BP on kidney cancer would be important for clinical interventions, including BP management program and kidney cancer screening guidelines for hypertensive individuals. Given these considerations, we conducted the present meta-analysis of prospective studies with the following objectives: to comprehensively review and summarize the relation of BP with risk of kidney cancer by using published prospective data, to examine association between BP and kidney cancer according to study characteristics, and to investigate and quantify the potential dose–response association between BP and risk of kidney cancer.

MATERIALS AND METHODS

Search strategy

The current meta-analysis was planned, conducted, and reported according to Preferred Reporting Items for

Journal of Hypertension 2017, 35:000–000

Department of Endocrinology and Metabolism, The First Affiliated Hospital of Soochow University, Suzhou, China

Correspondence to Bi-Min Shi, Department of Endocrinology and Metabolism, The First Affiliated Hospital of Soochow University, Suzhou 215006, China.
E-mail: shibimin@163.com

Received 2 October 2016 **Revised** 30 October 2016 **Accepted** 11 January 2017

DOI:10.1097/HJH.0000000000001286

Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. PubMed and Web of Science databases were searched for studies assessing the association between BP and kidney cancer through July 2016. The following search terms were employed to retrieve the relevant literature in the databases: (blood pressure OR hypertension OR high blood pressure OR systolic blood pressure OR diastolic blood pressure) AND (kidney cancer OR renal cancer OR kidney carcinoma OR renal carcinoma OR renal cell cancer OR renal pelvis cancer OR renal cell carcinoma OR renal pelvis carcinoma OR kidney neoplasm OR renal neoplasm OR kidney neoplasms OR renal neoplasms OR kidney tumor OR renal tumor OR kidney tumour OR renal tumour) AND (cohort OR prospective OR follow-up OR follow up OR observational study). The search strategy had no language, publication date, or publication type restriction. In addition, the reference lists of the retrieved full publications were reviewed to complement the search and to identify relevant studies that were missed during electronic database search. No attempt was made to identify unpublished studies.

Study selection

To be included in this meta-analysis, the studies had to meet the following inclusion criteria: the study design was a prospective study (including prospective cohort study, nested case–control study, and case–cohort study), the exposure was reported history of hypertension or recorded BP levels (SBP or DBP), the end point was kidney cancer incidence, and relative risks (RRs) or hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were available. Accordingly, retrospective studies, or studies on kidney cancer mortality or recurrence, were excluded. If one study was reported in overlapping publications, the publication containing more detailed information (i.e. reporting data for subgroup or dose–response analyses) was selected.

Data extraction and quality assessment

Using a standardized data collection form, the following data were abstracted from each study: the first author's last name, publication year, country, study population, mean age or age range of the participants, duration of follow-up, number of participants, sample sizes and number of cases, exposure variable either recorded BP levels or reported hypertension, the multivariable-adjusted risk estimates with their corresponding 95% CIs, and statistical adjustment for potential confounding factors. If multiple RRs of the association were available, we extracted RRs with their corresponding 95% CIs from the models that reflected the maximum extent of adjustment for potentially confounding variables. When studies provided specific risk estimates (i.e. sex), we extracted all of them and used the data in subgroup analysis. The study quality was assessed using the 9-star Newcastle–Ottawa Scale (NOS) [30], in which each study was judged based on the selection of the study groups (representativeness, selection of nonexposed cohort, ascertainment of exposure, and no disease at start of study), the comparability of the groups (assessment of outcome, length of follow-up, and adequacy of follow-up), and three for the quality of the outcome (assessment of outcome, length of follow-up, and adequacy of follow-up). Studies with NOS values of 6 or more were considered moderate-quality to high-quality studies and those with an NOS value of less than 6 were regarded low-quality studies. Two investigators (K.H. and X.D.) independently performed the literature search, studies selection, and data extraction. Any discrepancies regarding inclusion were solved through group discussion.

Statistical analysis

RR was chosen as the common measure of association across this study, HR and OR were directly considered as RR. DerSimonian and Laird [31] random-effects model was used to calculate the summary risk estimates. The degree of heterogeneity in the relationship between BP and kidney cancer across studies was assessed using Q and I^2 statistics. For the Q statistic, P value less than 0.1 was considered statistically significant; and for the I^2 statistic, the following conventional cutoff points were used: less than 25% (low heterogeneity), 25–50% (moderate heterogeneity), and more than 75% (severe heterogeneity). Both Begg's rank correlation test and Egger's linear regression test were performed to investigate potential publication bias [32]. If evidence of publication bias was observed, the trim and fill method was applied to correct the bias [33]. We performed subgroup and meta-regression analyses, according to duration of follow-up; sex of the participants (men/women); and adjusted for BMI (yes/no), smoking (yes/no), and hypertension (yes/no), to explore potential sources of heterogeneity across studies examining relationship between history of hypertension and kidney cancer. To investigate the impacts of individual studies on the overall results, we also performed a sensitivity analysis by omitting one study in each turn while pooling results from the remainder. We performed a linear dose–response analysis examining the association between BP and kidney cancer risk according to the method proposed by Greenland and Longnecker [34] and Orsini *et al.* [35]. This method requires the number of cases and person-years and the risk estimates with their variance estimates for at least three quantitative BP level categories. For the studies that did not provide the number of cases and/or person-years in each BP levels category, we estimated these data from total number of cases and person-years. For each study, the median or mean level of for each category was assigned to each corresponding risk estimate. When the median or mean BP levels per category were not provided, we considered the midpoint of the upper and lower boundaries in each category as new reference. If the highest or lowest category was open-ended, we assumed the width of the interval to be the same as in the closest category. Forest plots of the linear dose–response meta-analysis were presented for each 10-mmHg increase in SBP and DBP. A potential nonlinear relationship between BP and kidney cancer was examined by using fractional polynomial models [36]. We determined the best fitting second-order fractional polynomial regression model, defined as the one with the lowest deviance. The following knots were used in this analysis: SBP (110, 120, 130, 140, 150, 160, 170, and 180 mmHg) and DBP (60, 70, 80, 90, 100, 110, and 120 mmHg). The P value for nonlinearity was calculated

by testing the null hypothesis that the coefficient of the second spline is equal to 0. All statistical analyses were performed using STATA software, version 11.0 (STATA Corp., College Station, Texas, USA). All *P* values were two-sided, and the level of significance was less than 0.05, unless explicitly stated.

RESULTS

Literature search and study characteristics

A flowchart of study selection, including reasons for exclusion, is presented in Fig. 1. We included 18 [11–28] prospective studies that fully met our inclusion criteria for this meta-analysis. The characteristics of the included studies are summarized and listed in Table 1. Among the 18 included studies examining the relationship between BP and risk of kidney cancer, 11 studies [11,13,15,17–19,22, 24,26–28] used reported hypertension as the principal exposure variable, six [12,14,20,21,23,25] used recorded BP levels, and one [16] used both reported hypertension and recorded BP levels. These studies were published between 1990 and 2016. The number of kidney cancer cases diagnosed in these studies ranged from 14 to 895, with a total of 8097 of kidney cancer cases diagnosed among participants. The number of participants ranged from 2964 to 998 904, with a total of 3628 479 participants. Nine studies were conducted in the United States [11–13,15,17,19,24, 25,27], two [21,23] in multiple European countries, one [14] in Sweden, one [16] in Republic of Korea, one [20] in Norway, one [18] in Netherlands, one in Japan [22], one [28] in Iceland, and one in China [26]. Regarding the sex of the participants, three [12,14,16] were conducted exclusively in men, two [15,25] studies evaluated only women, and the remaining 13 [11,13,17–24,26–28] included both sexes. The length of follow-up ranged from 6 to 25 years. Three [13,15,16] studies adjusted for age only, whereas other studies adjusted for a wide range of potential confounding factors, such as age, BMI, and smoking. The details of quality assessment according to the 9-star NOS are presented in the online Supplementary Tables S1 and S2, http://links.lww.com/HJH/A733. All of these studies were given scores of at least 7.

Hypertension and kidney cancer

Twelve prospective studies [11,13,15,16–19,22,24,26–28] were eligible for the analysis of hypertension and risk of kidney cancer and included 5435 kidney cancer cases among 2170 265 participants. The summary RR for the association between history of hypertension and kidney cancer was 1.67 (95% CI 1.46, 1.90) with significant heterogeneity, $I^2 = 66\%$, *P* value less than 0.01 (Fig. 2). The observed statistically significant heterogeneity was mainly driven by heterogeneity between studies in men, as well as studies that did not adjust for BMI and hypertension. Overall, the findings from our subgroup analyses showed that duration of follow-up; sex of the participants; and adjustment for BMI, smoking, and hypertension did not materially alter the combined RRs (Table 2). The sensitivity analysis in which one study at a time was omitted generally showed statistically significant, with pooled RRs ranging from 1.66

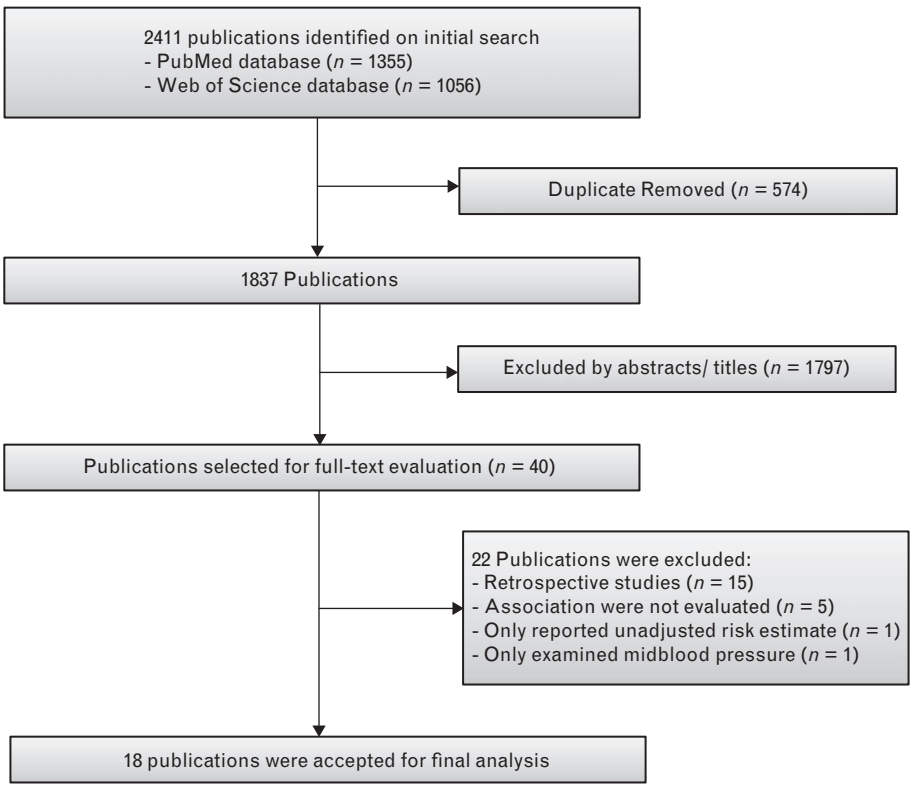

FIGURE 1 Flowchart of study selection of articles included in the current meta-analysis.

TABLE 1. Characteristics of studies included in the meta-analysis on the association of blood pressure and risk of kidney cancer

References (country)	Study population	Age: mean/ range (years)	Duration of follow-up (years)	Sample size (cases)	Exposure variables	Adjusted RR (95% CI)	Adjustments
Fraser *et al.* (USA) [11]	Non-Hispanic white men and women	≥25	6	34 198 (14)	HTN (yes vs. no)	2.9 (1.08, 10.27)	Age and sex
Grove *et al.* (USA) [12]	Japanese-American men	46–65	20	8006 (17)	Per 10-mmHg increase in blood pressure	SBP: 1.22 (1.00, 1.49); DBP: 1.47 (1.04, 2.08)	Age and pack-years of current smokers
Heath *et al.* (USA) [13]	Men and women	≥30	7	998 904 (335)	HTN (yes vs. no)	HTN M: 1.1 (0.9, 1.5); HTN W: 2.2 (1.5, 3.2)	Age
Chow *et al.* (Sweden) [14]	Swedish men	44.2	15	363 992 (895)	SBP: ≥160 vs. <120 mmHg; DBP: ≥110 vs. <70 mmHg	SBP for RCC: 1.7 (1.1, 2.6); DBP for RCC: 2.2 (1.1, 4.5); SBP for RPC: 0.7 (0.3, 1.5); DBP for RPC: 0.6 (0.1, 2.4)	Age, smoking status, BMI, and DBP
Nicodemus *et al.* (USA) [15]	Postmenopausal women	55–69	15	34 637 (124)	HTN (yes vs. no)	HTN: 1.68 (1.18, 2.39)	Age
Choi *et al.* (Republic of Korea) [16]	Korean men	≥30	7	576 562 (92)	HTN (yes vs. no); SBP: ≥160 vs. <120 mmHg; DBP: ≥100 vs. <80 mmHg	HTN: 2.5 (1.6, 3.8); SBP: 3.8 (1.7, 8.4); DBP: 3.9 (1.9, 8.0)	Age
Flaherty *et al.* (USA) [17]	Female nurses from the Nurses' Health Study; male health professional from the Health Professionals Follow-up Study	40–75 M; 30–35 W	24 W, 12 M	48 953 (110) M and 118 191 (155) W	HTN (yes vs. no)	HTN M: 1.8 (1.2, 2.7); HTN W: 1.9 (1.4, 2.7)	Age, BMI, and smoking
Schouten *et al.* (Netherlands) [18]	Men and women	55–69	11.3	4774 (337)	HTN (yes vs. no)	1.22 (0.94, 1.58)	Age, sex, BMI, current cigarette smoking, number of cigarettes smoked per day, and years of cigarette smoking
Setiawan *et al.* (USA) [19]	Men and women	45–75	8.3	161 126 (347)	HTN (yes vs. no)	HTN M: 1.42 (1.07, 1.87); HTN W: 1.58 (1.09, 2.28)	Age, BMI, smoking, alcohol drinking, hypertension, and physical activity
Vatten *et al.* (Norway) [20]	Men and women	53 M; 56 W	18	35 688 (144) M and 36 728 (94) W	SBP: ≥170 vs. <130 mmHg; DBP: ≥105 vs. <85 mmHg	SBP M: 1.0 (0.5, 1.9); DBP M: 0.9 (0.4, 2.0); SBP W: 2.0 (0.9, 4.6); DBP W: 1.6 (0.8, 3.5)	Age, BMI, smoking, and education
Weikert *et al.* (European countries) [21]	Men and women	52	6.2	296 638 (250)	SBP: ≥160 vs. <120 mmHg; DBP: ≥100 vs. <80 mmHg	SBP all: 2.48 (1.53, 4.02); DBP all: 2.34 (1.54, 3.55); SBP M: 2.42 (1.13, 5.19); DBP M: 3.11 (1.72, 5.62); SBP W: 2.62 (1.38, 4.97); DBP W: 1.87 (0.98, 3.57)	Age, sex, BMI, education, duration of smoking, smoking status, and antihypertensive medication use
Washio *et al.* (Japan) [22]	Japanese men and women	40–79	7.6	62 689 (40)	HTN (yes vs. no)	4.27 (2.07, 8.79)	Age and sex

TABLE 1 (*Continued*)

References (country)	Study population	Age: mean/ range (years)	Duration of follow-up (years)	Sample size (cases)	Exposure variables	Adjusted RR (95% CI)	Adjustments
Häggström *et al.* (Norway, Sweden, and Austria) [23]	Men and women	42	10	560 388 (855)	SBP M: 156.4 vs. 112.2 mmHg; DBP M: 95.5 vs. 66.9 mmHg; SBP W: 155.7 vs. 104 mmHg; DBP W: 92 vs. 61.3 mmHg	SBP M: 3.40 (1.91, 6.06); DBP M: 3.33 (1.85, 5.99); SBP W: 1.58 (0.60, 4.14); DBP W: 1.06 (0.43, 2.62)	Age, smoking, and BMI
Macleod *et al.* (USA) [24]	Men and women	50–76	8	77 260 (249)	HTN (yes vs. no)	1.70 (1.30, 2.22)	Age, sex, BMI, smoking, alcohol consumption, fruit intake, vegetable intake, hypertension, diabetes, kidney disease, and viral hepatitis
Sanfilippo *et al.* (USA) [25]	Participants from the Women's Health Initiative	50–79	10.8	156 774 (407)	SBP: >160 vs. ≤120 mmHg; DBP: >90.0 vs. ≤90 mmHg	SBP: 1.54 (0.96, 2.45); DBP: 1.56 (1.06, 2.29)	Age, BMI, smoking, diabetes, and race/ ethnicity
Shen *et al.* (China) [26]	Participants from the Shanghai Women's Health Study and Shanghai Men's Health Study	40–74 M; 40–70 W	12	2964 (271)	HTN (yes vs. no)	All: 1.4 (1.1, 1.90); M: 1.3 (0.9, 2.00); W: 1.5 (0.99, 2.3)	Education, smoking history, current alcohol drinking status, family history of cancer, and BMI
Hofmann *et al.* (USA) [27]	Members of Kaiser Permanente Northern California	18–99	10	31 167 (3136)	HTN (yes vs. no)	1.9 (1.7, 2.00)	Smoking and diabetes
Mariusdottir *et al.* (Iceland) [28]	Men and women	53	25	18 840 (225)	HTN (yes vs. no)	HTN: 1.46 (1.05, 2.03)	Age, sex, BMI, hypertension, kidney disease, smoking, and the five occupation (painter, aircraft mechanic, factory worker, shipbuilder, and housewife)

CI, confidence interval; HTN, hypertension; M, men; NA, not available; RCC, renal-cell cancer; RPC, renal-pelvis cancer; RR, relative risk; W, women.

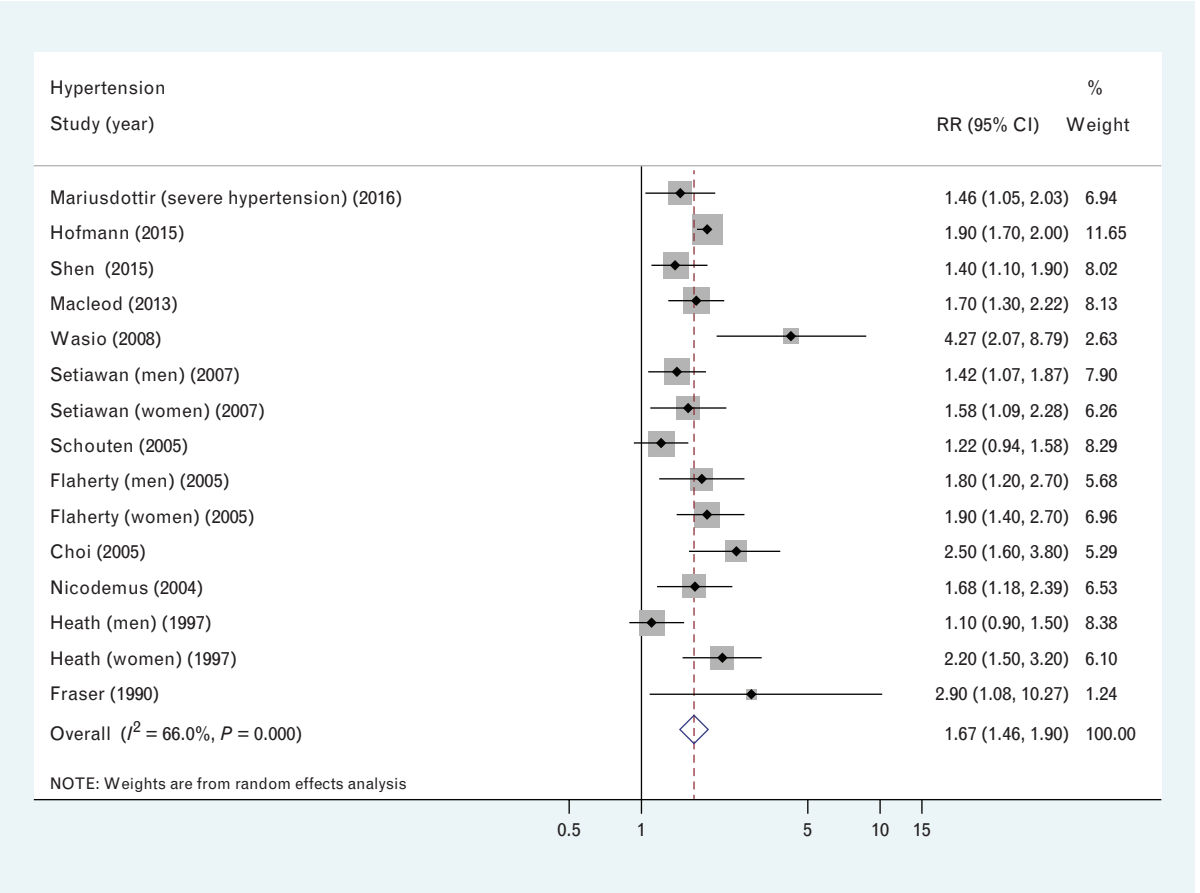

FIGURE 2 Forest plot for random-effects meta-analysis examining the association between hypertension and risk of kidney cancer.

(95% CI 1.44, 1.91) to 1.69 (95% CI 1.46, 1.96). Begg's test ($P = 0.015$) suggested the evidence of publication bias but not Egger's test ($P = 0.649$). However, the results remain unchanged after introducing the trim and fill method to correct the publication bias because no missing studies were detected to be filled.

Dose–response analysis

Seven prospective studies [12,14,16,20,21,23,25] were eligible for dose–response analysis and included 2754 kidney cancer cases among 2034 776 participants. Each 10-mmHg increase in SBP was associated with 11 (RR 1.11, 95% CI 1.06, 1.17), 9 (RR 1.09, 95% CI 1.03, 1.16),

TABLE 2. Subgroup analyses of hypertension and kidney cancer

Subgroup	Diagnosis of hypertension or history of hypertension				
	Studies (*n*)	RR (95% CI)	I^2 (%)	*P*	*P**
Follow-up					
≥10 years	6	1.61 (1.38, 1.89)	60.6	0.019	0.560
<10 years	6	1.81 (1.41, 2.33)	71	<0.01	
Sex					
Men	5	1.51 (1.16, 1.97)	66.4	0.018	0.402
Women	5	1.77 (1.50, 2.08)	0	0.646	
Adjusted for BMI					
Yes	6	1.51 (1.36, 1.68)	0	0.480	0.165
No	6	1.94 (1.50, 2.51)	76	<0.01	
Adjusted for smoking					
Yes	7	1.60 (1.40, 1.81)	55.1	0.023	0.278
No	5	2.05 (1.39, 3.02)	78.3	<0.01	
Adjusted for hypertension					
Yes	3	1.54 (1.32, 1.79)	0	0.809	0.480
No	9	1.75 (1.46, 2.08)	73.2	<0.01	

P value for heterogeneity. CI, confidence interval; RR, relative risk.
**P* value for heterogeneity between groups according to meta-regression.

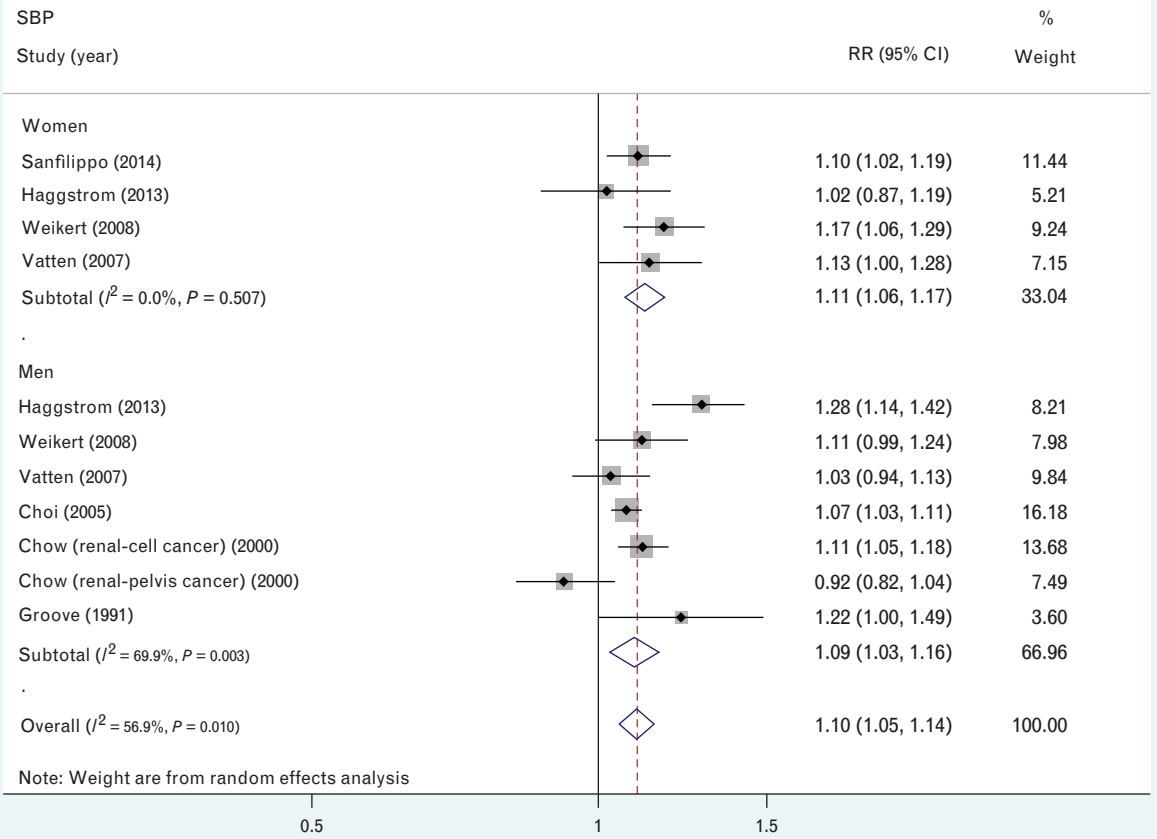

FIGURE 3 Linear dose–response analysis on systolic blood pressure and kidney cancer risk, per 10 mmHg increase. CI, confidence interval; RR, relative risk.

and 10% (RR 1.10, 95% CI 1.05, 1.14) (Fig. 3) increased risks of kidney cancer in women, men, and women and men combined, respectively. Furthermore, each 10-mmHg increment in DBP was associated with 16 (RR 1.16, 95% CI 1.02, 1.31), 25 (RR 1.25, 95% CI 1.09, 1.43), and 22% (RR 1.22, 95% CI 1.10, 1.34) increased risks of kidney cancer in women, men, and women and men combined, respectively (Fig. 4). We found statistically significant heterogeneity between studies among men (SBP: $I^2 = 69.9\%$, $P < 0.01$; DBP: $I^2 = 74.8\%$, $P < 0.01$), whereas no heterogeneity was observed between studies among women (SBP: $I^2 = 0\%$, $P = 0.507$; DBP: $I^2 = 0\%$, $P = 0.679$). There is evidence of nonlinear dose–response relations for SBP (P for nonlinearity <0.001) (Fig. 5) and DBP (P for nonlinearity = 0.001) (Fig. 6), with noticeable increase in risk for SBP of 150 mmHg or a DBP of 100 mmHg, whereas the range below these thresholds risk rose rather mildly but steadily with increasing BP. Results of the sensitivity analysis indicated that the overall risk estimates were not dominated by any single study, with summary RRs ranging from 1.09 (95% CI 1.04, 1.14) to 1.11 (95% CI 1.06, 1.16) for SBP and 1.20 (95% CI 1.08, 1.33) to 1.27 (95% CI 1.14, 1.42) for DBP. Both Begg's rank correlation test ($P > 0.5$) and Egger's regression test ($P > 0.5$) did not indicate the evidence of publication bias.

DISCUSSION

The present meta-analysis of 18 prospective studies provides further support for a positive association between hypertension and kidney cancer. Dose–response analysis revealed that each 10-mmHg increase in SBP and DBP were significantly associated with 10 and 22% increased risk of kidney cancer, respectively. Regarding the sex of participants, several prospective studies have shown a convincing exposure–response relationship between BP levels and kidney cancer risk among men [14,16,21,23]. On the other hand, the results were less consistent among women [20,21,23,25]. Nevertheless, we found a positive dose–response relationship in both sexes.

The biological mechanisms underlying the relationship between hypertension and kidney cancer remain unclear, but are hypothesized to involve chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species [37,38]. Hypertensive individuals may suffer chronic renal hypoxia caused by the transcription of hypoxia-inducible factors that promote tumor cell proliferation and angiogenesis [39]. There are ample of evidence that obese individuals are at a high risk of kidney cancer [9]. Similarly, numerous observational studies have consistently reported that hypertensive individuals experience an increased risk

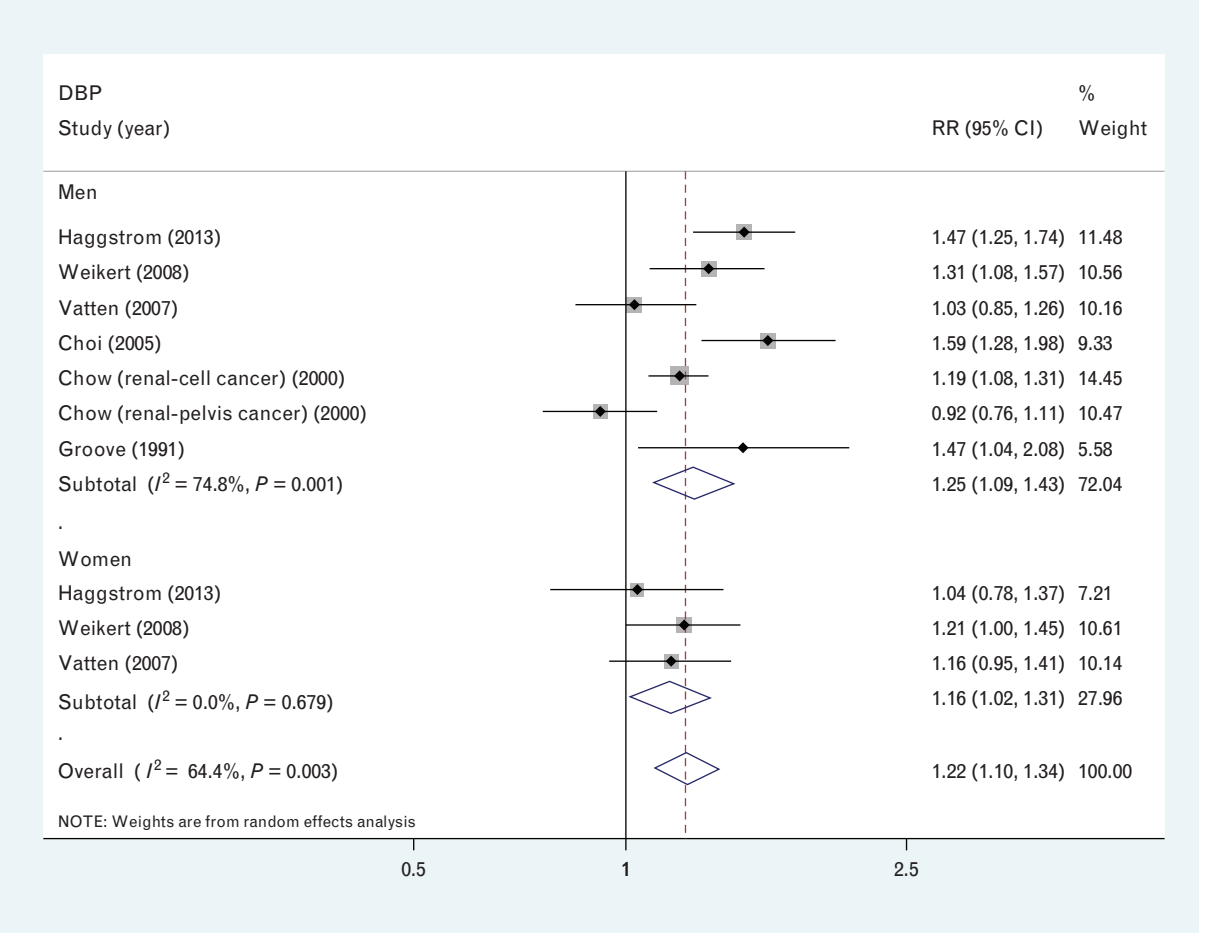

FIGURE 4 Linear dose–response analysis on diastolic blood pressure and kidney cancer risk, per 10 mmHg increase. CI, confidence interval; RR, relative risk.

of kidney cancer [14,16]. Obesity and hypertension are both associated with lipid disturbances [40]. Individuals with high BMI and those with elevated hypertension also exhibit increased lipid peroxidation, which has been implicated in the pathogenesis of kidney cancer [41–43]. Experimental studies suggest that lipid peroxidation of the proximal renal tubules play a critical role in chemically induced renal carcinogenesis [44–48]. Byproducts of lipid peroxidation have been shown to react with renal DNA to form adducts [49,50]. Misrepair of the DNA damaged by these adducts leading to mutations in protooncogenes and/or tumor suppressor genes, which is a critical step in the generation and progression of changing a normal cell to a malignant phenotype [37,51]. Despite the high correlation between obesity and hypertension, their associations with kidney cancer risk have been shown to be independent of each

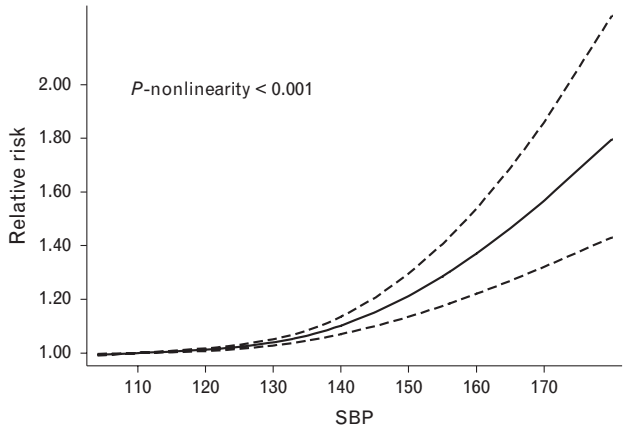

FIGURE 5 Nonlinear dose–response relations between systolic blood pressure and kidney cancer risk.

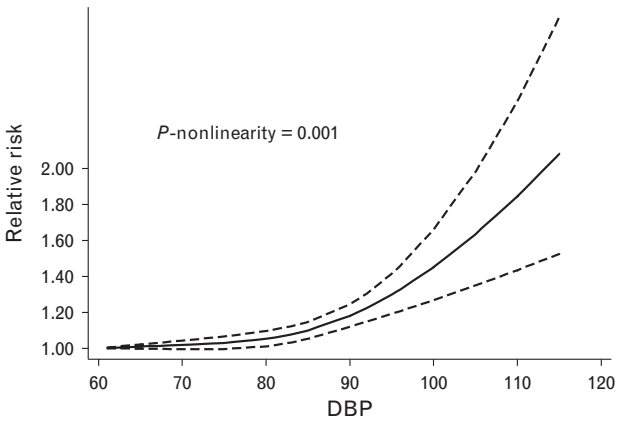

FIGURE 6 Nonlinear dose–response relations between diastolic blood pressure and kidney cancer risk.

other [14,19,21,25]. Concordantly, findings from our stratified analyses showed that hypertension increases the risk of kidney cancer independently of obesity (as measured by BMI). The risk to suffer from kidney cancer is higher among individuals who are both obese and have hypertension than those who have one of these risk factors [14,19,21,25].

Association between hypertension and cancer has been examined in several observational studies [52,53]. A meta-analysis based on 10 longitudinal studies of in total 47 119 participants showed that hypertension was related to a 23% increased risk of cancer mortality [52]. Moreover, the largest study to date consisting over half a million participants from the Metabolic Syndrome and Cancer Project with a median follow-up of 12 years found a small increased of total cancer risk in men with elevated BP level and a higher risk for cancer mortality in both sexes. In this study, the association between hypertension and cancer incidence has also been found to differ by cancer sites [53]. Both hypertension and cancer are possible consequences of similar risk factors, such as cigarette smoking, diabetes, obesity, alcohol consumption, physical inactivity, and environmental/occupational exposure [54–56]. For example, obesity, diabetes, hypertension, and cancer have a complex relationship, which is mediated by several common factors such as diet, body fat distribution, physical activity, hyperglycemia, insulin and insulin-like growth factor signaling, adipokines, sex hormones, inflammation, and oxidative stress [54]. Regarding cigarette smoking, carcinogens, irritants, proinflammatory stimuli, and oxidizing agents contained in cigarette are thought to play an important role in the development of both cancer and hypertension [54]. Furthermore, environmental factors such as heavy metals exposure have also been linked to increased risk of cancer and hypertension [57,58]. Given these considerations, it is not surprising that the association between hypertension and kidney cancer is not only complex but also subject to similar confounding factors shared by both conditions. Our findings showed a robust association between hypertension and increased kidney cancer risk independent of BMI and smoking. However, further clarification for the issue of whether hypertension itself is associated with increased risk of kidney cancer, rather than a proxy for another cancer risk factor, is needed.

The relationship between hypertension, antihypertensive medications, and the risk of kidney cancer remains controversial, given most investigations were based on diagnosis of hypertension that is inevitably linked to antihypertensive medications use. On the basis of our findings, it is expected that antihypertensive treatment would reduce the risk of kidney cancer. Conversely, a recent study by Sanfilippo *et al.* [25] showed that higher rates of kidney cancer were observed among women with treated hypertension than among untreated hypertension. These findings potentially suggest that antihypertensive medications may contribute in the development of kidney cancer. Nonetheless, adjustment for hypertension appears to attenuate excess risk for kidney cancer associated with antihypertensive medications use in several studies [59,60]. Furthermore, study by Weikert *et al.* showed that both elevated SBP and DBP were positively associated with kidney cancer risk that was independent of antihypertensive medications use. The authors also suggest that among individuals taking antihypertensive drugs, only those who had poorly controlled BP showed a significantly increased kidney cancer risk [21]. Thus far, most studies have concluded that associations between antihypertensive drugs and kidney cancer are unlikely to be causal, but rather reflecting confounding, from failure to control the preexisting hypertension [14,21,61]. Altogether, the risk of kidney cancer could be modified with better BP control. Further large prospective studies focusing on the influence of treatment of hypertension on this association are needed.

As mentioned earlier, Europe and North America have the highest incidence of kidney cancer in the world, whereas Asia and Africa have the lowest incidence [1,3,4]. Geographic disparities in incidence rates may be due to heredity, differences in diagnostic imaging frequency and technology, healthcare access and quality, as well as prevalence of environmental and lifestyle-related risk factors. In the last few decades, the incidence rates of kidney cancer have risen more rapidly among blacks than among whites and are higher among blacks than among whites in the United States [62]. The reasons for these racial disparities in incidence are unclear, though hypertension may also play a role in these racial disparities; hypertension, which is one of well established risk factors for kidney cancer, is also more frequent among blacks than whites [2]. Two observational studies have investigated the association between hypertension and kidney cancer risk for blacks and whites [27,63]. A population-based case–control study found that hypertension nearly doubled and tripled the risk of developing kidney cancer among whites and blacks, respectively [27]. Moreover, a nested case–control study, investigating kidney cancer risk factors across racial/ethnic groups (white, black, Hispanic, and Asian/Pacific Islander), found hypertension to be positively associated with kidney cancer, but findings did not substantially differ by race. However, blacks had the highest proportion of hypertension-related kidney cancer incidence compared with other racial/ethnic groups [63]. Based on these findings, hypertension has the strongest effect in blacks than other racial/ethnic groups and might partially explain the racial disparity in kidney cancer incidence in the United States. Furthermore, several epidemiologic studies conducted in Asian populations also found an increased kidney cancer risk associated with hypertension [16,26,64]. Nevertheless, data on an association between race/ethnicity and kidney cancer risk remain inconclusive. Therefore, more prospective studies assessing potential disparities between racial/ethnic groups on the association between hypertension and kidney cancer risk are needed.

To our knowledge, we report the first dose–response meta-analysis of the association between BP and incident kidney cancer. The present study has several strengths, including incorporated evidence and relevant studies to the date. The enlarged sample size enhanced the power to detect a significant difference and provide more precise estimates of the effects. Most of the original studies included are of long follow-up durations, and all studies used a prospective design that thereby reduced the likelihood of potential biases (i.e., recall and selection biases) and reverse causality.

There are several limitations in the present meta-analysis that should be acknowledged. First, there was evidence of publication bias. Second, there was significant heterogeneity among included studies, which was not surprising given the differences in the strength of the association, duration of follow-up, sample sizes, population characteristics, and statistical adjustments for potential confounders. Our stratified analyses indicated that studies conducted among women and studies that adjusted for BMI and hypertension are homogenous. Furthermore, the observed heterogeneity may be due to differences in the strength of the association, rather than due to differences in the directionality of effect as all studies showed a clear trend toward increased risk of kidney cancer. Third, there was lack of adjustment for confounding factors in several included studies and thus may bias the findings toward exaggeration or underestimation of risk estimates. In addition, the potential impacts of confounding by unknown or unmeasured factors on our findings cannot be completely excluded. Given the evidence of publication bias, heterogeneity, and lack of adjustments for confounders among studies, the results from our meta-analysis should always be treated with caution. Fourth, given of the rarity of kidney cancer, small numbers of cases among included studies may have led to null association that might have otherwise. Fifth, the possible dose–response meta-analysis measurement error should also be acknowledged, as it requires assumptions such as approximating the width of the open-ended lowest and highest boundaries from the closest category and assigning the midpoint of each category to corresponding RR. Finally, almost all of the included studies were conducted in well developed Western countries (Europe and North America) where the incidence of kidney cancer is higher than in less-developed countries. Thus, our findings may not be generalized to other populations. More prospective studies conducted in other continents, particularly in Asia and Africa, are needed to confirm and extent our findings.

In conclusion, the current meta-analysis of 18 prospective studies provides further support for a positive association between hypertension and kidney cancer. Providing a better understanding of the cause and pathogenesis of kidney cancer is essential for developing treatment and prevention strategies in this era of increasing incidence. Given that hypertension is a major modifiable risk factor and its control remains inadequate, the findings from our meta-analysis highlight the need and importance of current public health strategies aimed at preventing and effectively controlling hypertension to reduce the incidence of a number of diseases related to elevated BP including kidney cancer. Further prospective studies focusing on the influence of antihypertensive treatments and race/ethnicity on this association are also needed. In addition, more experimental studies are warranted to better delineate underlying biological mechanisms of this association.

ACKNOWLEDGEMENTS

Authors' contributions: K.H. contributed to the study design, literature search, data extraction, data analyses, and writing the article. X.D. assisted with literature search and selection. X.D. and S.-Y.Z. provided statistical support and created all tables and figures. B.-M.S. critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

The study was supported by grants from the Suzhou Social Development Fund nos. SYSD2013080 and SYS201455.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359–E386.
2. Chow W, Devesa S, Warren J, Fraumeni J Jr. Rising incidence of renal cell cancer in the United States. *JAMA* 1999; 281:1628–1631.
3. Weikert S, Ljungberg B. Contemporary epidemiology of renal cell carcinoma: perspectives of primary prevention. *World J Urol* 2010; 28:247–252.
4. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010; 7:245–257.
5. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, *et al*. The epidemiology of renal cell carcinoma. *Eur Urol* 2011; 60:615–621.
6. Moore LE, Wilson RT, Campleman SL. Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review. *Cancer Invest* 2005; 23:240–255.
7. Bergstrom A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A. Obesity and renal cell cancer – a quantitative review. *Br J Cancer* 2001; 85:984–990.
8. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *Int J Cancer* 2005; 114:101–108.
9. Wang F, Xu Y. Body mass index and risk of renal cell cancer: a dose–response meta-analysis of published cohort studies. *Int J Cancer* 2014; 135:1673–1686.
10. Radišauskas R, Kuzmickienė I, Milinavičienė E, Everatt R. Hypertension, serum lipids and cancer risk: a review of epidemiological evidence. *Medicina (Kaunas)* 2016; 52:89–98.
11. Fraser GE, Phillips RL, Beeson WL. Hypertension, antihypertensive medication and risk of renal carcinoma in California Seventh-Day Adventists. *Int J Epidemiol* 1990; 19:832–838.
12. Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol* 1991; 134:942–947.
13. Heath CW Jr, Lally CA, Calle EE, McLaughlin JK, Thun MJ. Hypertension, diuretics, and antihypertensive medications as possible risk factors for renal cell cancer. *Am J Epidemiol* 1997; 145:607–613.
14. Chow WH, Gridley G, Fraumeni JF Jr, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 2000; 343:1305–1311.
15. Nicodemus KK, Sweeney C, Folsom AR. Evaluation of dietary, medical and lifestyle risk factors for incident kidney cancer in postmenopausal women. *Int J Cancer* 2004; 108:115–121.
16. Choi MY, Jee SH, Sull JW, Nam CM. The effect of hypertension on the risk for kidney cancer in Korean men. *Kidney Int* 2005; 67:647–652.
17. Flaherty KT, Fuchs CS, Colditz GA, Stampfer MJ, Speizer FE, Willett WC, Curhan GC. A prospective study of body mass index, hypertension, and smoking and the risk of renal cell carcinoma (United States). *Cancer Causes Control* 2005; 16:1099–1106.
18. Schouten LJ, van Dijk BA, Oosterwijk E, Hulsbergen-van de Kaa CA, Kiemeney LA, Goldbohm RA, *et al*. Hypertension, antihypertensives and mutations in the Von Hippel–Lindau gene in renal cell carcinoma: results from the Netherlands Cohort Study. *J Hypertens* 2005; 23:1997–2004.
19. Setiawan VW, Stram DO, Nomura AM, Kolonel LN, Henderson BE. Risk factors for renal cell cancer: the multiethnic cohort. *Am J Epidemiol* 2007; 166:932–940.
20. Vatten LJ, Trichopoulos D, Holmen J, Nilsen TI. Blood pressure and renal cancer risk: the HUNT Study in Norway. *Br J Cancer* 2007; 97:112–114.

21. Weikert S, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, *et al.* Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Am J Epidemiol* 2008; 167:438–446.
22. Washio M, Mori M, Sakauchi F, Watanabe Y, Ozasa K, Hayashi K, *et al.* Hypertension and other risk factors for the development of kidney cancer (renal cell carcinoma) in a Japanese population: findings from the JACC study. *Int Med J* 2008; 15:343–347.
23. Häggström C, Rapp K, Stocks T, Manjer J, Bjørge T, Ulmer H, *et al.* Metabolic factors associated with risk of renal cell carcinoma. *PLoS One* 2013; 8:e57475.
24. Macleod LC, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, White E. Risk factors for renal cell carcinoma in the VITAL study. *J Urol* 2013; 190:1657–1661.
25. Sanfilippo KM, McTigue KM, Fidler CJ, Neaton JD, Chang Y, Fried LF, *et al.* Hypertension and obesity and the risk of kidney cancer in 2 large cohorts of US men and women. *Hypertension* 2014; 63:934–941.
26. Shen T, Shu XO, Xiang YB, Li HL, Cai H, Gao YT, *et al.* Association of hypertension and obesity with renal cell carcinoma risk: a report from the Shanghai Men's and Women's Health Studies. *Cancer Causes Control* 2015; 26:1173–1180.
27. Hofmann JN, Corley DA, Zhao WK, Colt JS, Shuch B, Chow WH, Purdue MP. Chronic kidney disease and risk of renal cell carcinoma: differences by race. *Epidemiology* 2015; 26:59–67.
28. Mariusdottir E, Ingimarsson JP, Jonsson E, Einarsson GV, Aspelund T, Gudnason V, Gudbjartsson T. Occupation as a risk factor for renal cell cancer: a nationwide, prospective epidemiological study. *Scand J Urol* 2016; 50:181–185.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6:e1000097.
30. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses; 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (Accessed March 2016).
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:177–188.
32. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634.
33. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56:455–463.
34. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. *Am J Epidemiol* 1992; 135:1301–1309.
35. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. *Stata J* 2006; 6:40–57.
36. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose–response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* 2012; 175:66–73.
37. Sharifi N, Farrar WL. Perturbations in hypoxia detection: a shared link between hereditary and sporadic tumor formation? *Med Hypotheses* 2006; 66:732–735.
38. Gago-Dominguez M, Castelao JE, Yuan JM, Ross RK, Yu MC. Lipid peroxidation: a novel and unifying concept of the etiology of renal cell carcinoma (United States). *Cancer Causes Control* 2002; 13:287–293.
39. Kaelin WG Jr. The von Hippel–Lindau gene, kidney cancer, and oxygen sensing. *J Am Soc Nephrol* 2003; 14:2703–2711.
40. Gago-Dominguez M, Castelao JE. Lipid peroxidation and renal cell carcinoma: further supportive evidence and new mechanistic insights. *Free Radic Biol Med* 2006; 40:721–733.
41. Kumar KV, Das UN. Are free radicals involved in the pathobiology of human essential hypertension? *Free Radic Res Commun* 1993; 19:59–66.
42. Keidar S, Kaplan M, Shapira C, Brook JG, Aviram M. Low density lipoprotein isolated from patients with essential hypertension exhibits increased propensity for oxidation and enhanced uptake by macrophages: a possible role for angiotensin II. *Atherosclerosis* 1994; 107:71–84.
43. Van Gaal LF, Vertommen J, De Leeuw IH. The in vitro oxidizability of lipoprotein particles in obese and nonobese subjects. *Atherosclerosis* 1998; 137 (Suppl):S39–S44.
44. Li JL, Okada S, Hamazaki S, Ebina Y, Midorikawa O. Subacute nephrotoxicity and induction of renal cell carcinoma in mice treated with ferric nitrilotriacetate. *Cancer Res* 1987; 47:1867–1869.
45. Okada S, Hamazaki S, Ebina Y, Li JL, Midorikawa O. Nephrotoxicity and its prevention by vitamin E in ferric nitrilotriacetate-promoted lipid peroxidation. *Biochim Biophys Acta* 1987; 922:28–33.
46. Toyokuni S, Uchida K, Okamoto K, Hattori-Nakakuki Y, Hiai H, Stadtman ER. Formation of 4-hydroxy-2-nonenal-modified proteins in the renal proximal tubules of rats treated with a renal carcinogen, ferric nitrilotriacetate. *Proc Natl Acad Sci U S A* 1994; 91:2616–2620.
47. Toyokuni S, Luo XP, Tanaka T, Uchida K, Hiai H, Lehotay DC. Induction of a wide range of C(2–12) aldehydes and C(7–12) acyloins in the kidney of Wistar rats after treatment with a renal carcinogen, ferric nitrilotriacetate. *Free Radic Biol Med* 1997; 22:1019–1027.
48. Toyokuni S. Iron-induced carcinogenesis: the role of redox regulation. *Free Radic Biol Med* 1996; 20:553–566.
49. Umemura T, Sai K, Takagi A, Hasegawa R, Kurokawa Y. Formation of 8-hydroxydeoxyguanosine (8-OH-dG) in rat kidney DNA after intraperitoneal administration of ferric nitrilotriacetate (Fe-NTA). *Carcinogenesis* 1990; 11:345–347.
50. Toyokuni S, Mori T, Dizdaroglu M. DNA base modifications in renal chromatin of Wistar rats treated with a renal carcinogen, ferric nitrilotriacetate. *Int J Cancer* 1994; 57:123–128.
51. Umemura T, Hasegawa R, Sai-Kato K, Nishikawa A, Furukawa F, Toyokuni S, *et al.* Prevention by 2-mercaptoethane sulfonate and *N*-acetylcysteine of renal oxidative damage in rats treated with ferric nitrilotriacetate. *Jpn J Cancer Res* 1996; 87:882–886.
52. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? *Am J Med* 2002; 112:479–486.
53. Stocks T, Van Hemelrijck M, Manjer J, Bjørge T, Ulmer H, Hallmans G. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. *Hypertension* 2012; 59:802–810.
54. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation* 2016; 133:1104–1114.
55. Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, *et al.* Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation* 2004; 109:3244–3255.
56. Messerli FH. Risk factors for renal cell carcinoma: hypertension or diuretics? *Kidney Int* 2005; 67:774–775.
57. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. *Interdiscip Toxicol* 2014; 7:60–72.
58. Alissa EM, Ferns GA. Heavy metal poisoning and cardiovascular disease. *J Toxicol* 2011; 2011:870125.
59. Lipworth L, Tarone RE, McLaughlin JK. The epidemiology of renal cell carcinoma. *J Urol* 2006; 176:2353–2358.
60. Shapiro JA, Williams MA, Weiss NS, Stergachis A, LaCroix AZ, Barlow WE. Hypertension, antihypertensive medication use and risk of renal cell carcinoma. *Am J Epidemiol* 1999; 149:521–530.
61. Friis S, Sorensen HT, Mellemkjaer L, McLaughlin JK, Nielsen GL, Blot WJ, Olsen JH. Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based cohort study in Denmark. *Cancer* 2001; 92:2462–2470.
62. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. *Cancer J* 2008; 14:288–301.
63. Colt JS, Schwartz K, Graubard BI, Davis F, Ruterbusch J, DiGaetano R, *et al.* Hypertension and risk of renal cell carcinoma among white and black Americans. *Epidemiology* 2011; 22:797–804.
64. McLaughlin JK, Gao YT, Gao RN, Zheng W, Ji BT, Blot WJ, Fraumeni JF Jr. Risk factors for renal-cell cancer in Shanghai, China. *Int J Cancer* 1992; 52:562–565.

Reviewers' Summary Evaluations

Reviewer 1

The study presented a meta-analysis on the relationship between hypertension and the risk to develop kidney cancer. The authors found a significantly increased risk linearly related to SBP value. Several hypothesis about the association has been commented, including chronic renal hypoxia and lipid peroxidation, although the possibility that both cancer and hypertension can be the consequence of exposition to similar risk factors such as cigarette smoking, diabetes, obesity, alcohol consumption, physical inactivity, and environmental/occupational exposure for example environmental metals. The possible association, however, do not permit to take practical decisions in order to reduce risk of cancer as the authors concluded.

Reviewer 2

While this meta-analysis of uncontrolled observational studies reporting that history of hypertension is associated with increased risk of renal cancer is plausible, there are some concerns which warrant cautious interpretation of the findings. There was lack of adjustments for confounders in the individual studies or in the overall study, there was a high degree of heterogeneity leading to wide confidence intervals levels. A high degree of publication bias may also be present despite the authors' attempts at statistical adjustments.